CHAPTER 5

SEASONAL VARIATIONS IN HOUSE DUST MITE INFLUENCES THE CIRCADIAN PEAK EXPIRATORY FLOW AMPLITUDE

Gerda G Meijer[1], Dirkje S Postma[2], Sicco van der Heide[3], Dorothea M de Reus[1], Gerard H Koëter[2], Ruurd J Roorda[4], Wim MC van Aalderen[1]

[1] Department of Pediatric Pulmonology, Beatrix Children's Hospital
[2] Department of Pulmonology
[3] Department of Allergology
University Hospital Groningen
[4] Department of Pediatric Pulmonology
Hospital 'de Weezenlanden', Zwolle
The Netherlands

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Summary

The aim of the study was to investigate whether seasonal differences in house dust mite (HDM) allergen exposure influence the circadian peak expiratory flow (PEF) amplitude in asthmatic children. Asthmatic children (n = 25) with a solitary allergy to HDM were studied in spring and in autumn. All used inhaled corticosteroids (ICS) regularly. Six days after withdrawal of ICS PEF amplitude (every 4 h during 24 h, highest minus lowest as a percentage of day's mean value) was assessed. HDM allergen (HDMA) in living rooms, bedrooms and mattresses were collected. HDMA levels were not always highest in autumn. PEF amplitudes in spring and autumn did not correlate with HDMA levels in the same season. However, the seasonal difference in PEF amplitude (autumn value minus spring value) correlated positively and significantly with the seasonal difference in HDMA exposure levels from the mattresses (rho = 0.34, $p < 0.05$). Multivariate analysis showed that the seasonal difference in HDMA exposure in the mattress was the single parameter explaining seasonal difference in PEF amplitudes by 21.0% ($p = 0.02$). Our cross-sectional study showed a higher PEF amplitude not to be significantly associated with higher HDMA exposure in mattresses in a group of HDM-allergic asthmatic children. However, the change in HDMA exposure over seasons contributed significantly to the change in PEF amplitude after withdrawal of ICS in HDM-allergic asthmatic children.

Introduction

Natural indoor exposure to house dust mites (HDM) allergens is known to vary from season to season (1), although its variation is much less pronounced than exposure to pollen allergens. HDM inhalation in HDM-allergic individuals may result in an early and late asthmatic response, often followed by increased airway obstruction for many nights (2,3). Reduction of environmental allergens has been shown to improve the disease (4), and may result in a decrease of the circadian peak expiratory flow amplitude.

Little data are available with respect to the influence of a change in natural exposure levels of HDM allergens (HDMA) on clinical relevant variables. Although many clinicians in our part of the world have the impression that asthma deteriorates during autumn in many patients, the HDM season, it is not known whether seasonal variations in exogenous stimuli such as HDMA levels are associated with seasonal differences in PEF amplitude. In an earlier study we have found that exogenous factors such as HDMA exposure, environmental tobacco smoke and the presence of pets contributed to the magnitude of the circadian PEF amplitude measured in one season of the year (5).

In this study we further explored whether the seasonal difference in HDMA

exposure contributes to an increase in circadian PEF amplitude in asthmatic children with a mono-allergy to HDM.

Methods

Patients

Twenty-five asthmatic children (17 boys, 8 girls) aged 6 to 12 yrs were included. All were characterized by symptoms of asthma, increased total serum IgE, and specific IgE to HDM (RAST class ≥ 3, Pharmacia Diagnostics, Uppsala, Sweden). Children with other allergies proven by a positive RAST test were excluded in order to obtain a homogeneous population. All children had a forced expiratory volume in one second (FEV_1) of at least 70% of the predicted value, and increased bronchial responsiveness (histamine provocation concentration ≤ 8 mg/ml causing a fall of 20% or more in FEV_1 from baseline value). All children used inhaled corticosteroids (ICS) as maintenance medication, twice daily 200 or 400 µg, for at least 4 mo before the study and short-acting ß$_2$-adrenergic drugs when needed. None of the children used long-acting ß$_2$-adrenergic drugs. Routine standardized information with regard to reduction of environmental stimuli was given previously by pediatricians and/or nurses at our outpatient clinic. Acaricides, mattress encasings and dehumidifiers were not used in the investigated houses. Informed consent from all children and their parents was obtained, and the study was approved by the Medical Ethics Committee of our hospital.

Study Design

The same measurements were performed in all children both once in spring (March to May) and once in autumn (August to November). Children were included either in the spring or in autumn. To complete the group, children were included during three consecutive years. Seasonal differences were defined as the autumn value minus the spring value.

Daytime and nighttime symptoms were recorded in a 3-wk period during regular treatment with ICS and on the sixth day after withdrawal of ICS. At the end of the 3-wk period, a home and school visit was made to collect house dust from floors of living rooms and bedrooms and from mattresses. Temperature and relative humidity were measured in each location to obtain absolute humidity (gram water vapor per kilogram of dry air). A histamine challenge test was performed and a blood sample was drawn during ICS use at the outpatient clinic to determine bronchial responsiveness, the eosinophil count, total IgE, and specific IgE to HDM. FEV_1 during and at the sixth day after withdrawal of ICS was performed at the outpatient clinic. The circadian PEF amplitude (every 4 h during 24 h, expressed as highest minus lowest PEF value expressed as a percentage of the day's mean value) was obtained at home on the sixth day after withdrawal of ICS.

Clinical Characteristics

SYMPTOMS: Symptoms of cough, wheeze, dyspnea and phlegm production during the day and at night were recorded in a diary on a 4-point scale (0: no symptoms, 1: mild, 2: moderate, 3: severe) (6). Daytime and nighttime symptoms were recorded and added up during the 3-wk period to obtain the total symptom score at daytime and nighttime during ICS. Symptoms were also recorded during daytime and nighttime on the sixth day after withdrawal of ICS.

LUNG FUNCTION AND BRONCHIAL RESPONSIVENESS: Short-acting $ß_2$-adrenergic drugs were withheld 8 h before the measurements. PEF measurements were performed at home, every 4 h during 24 h, in an upright position with a mini-Wright peak flow meter to assess the circadian PEF amplitude. The best of three efforts was used for statistical analysis. FEV_1 was measured with a water-sealed spirometer (Lode BV, Groningen, the Netherlands). At least three reproducible values (i.e. < 5 percent difference among the recordings) were obtained; the highest was used in the analysis. Airway histamine challenge tests were performed during ICS with a gauged DeVilbiss 646 nebulizer (DeVilbiss, Somerset, MA, USA), with an output of 0.13 ml/min according to the modified method of Cockcroft and colleagues (7). A 0.9% phosphate-buffered saline solution and doubling histamine concentrations from 0.03 to 16 mg/ml were inhaled for two minutes during tidal breathing, with the nose clipped, at 5 min intervals, until FEV_1 had fallen by at least 20% from the initial value. The exact provocation concentration of histamine that induced a 20% fall in FEV_1 (PC_{20}) was assessed by a log-dose response curve.

Laboratory Investigations

Total IgE and specific IgE were quantified using an enzyme immunoassay procedure (Pharmacia Diagnostics), and expressed in international units (IU) per milliiter, and Phadebas RAST units (PRU) per milliliter, respectively.

House Dust Mite Allergen Exposure

All dust samples were obtained by the same technician, using a vacuum cleaner (Phillips type T580, 1100 W). For every location we used a different double-walled disposable paper bag (8), and a special vacuum cleaner filter for the mattresses (ALK filter device; surface, 38 cm^2, pore size, 6 µm; ALK, Hørsholm Denmark). Dust was collected from the total area of the location in order to obtain a representative sample. The total amount of fine dust of each floor sample was measured after filtering with a 355-µm aperture sieve. Each sample was analyzed for the amount of HDMA (*Der* p I and *Der* p II) per gram of fine dust according to the WHO International standards (9,10). After extraction of the dust samples, HDMA was analyzed by sandwich immunoassay using monoclonal antibodies (1).

Statistical Analysis

FEV_1 values were expressed as percentage of the predicted value (% pred) (11). PC_{20} values were used after logarithmic transformation (base 2), since these reflect doubling doses and a normalized distribution. In subjects who did not reach a 20% fall in FEV_1 after the maximum exposure of 16 mg/ml histamine (spring n = 4), PC_{20} was considered to be one doubling doses higher (32 mg/ml). Total IgE and specific IgE HDM were logarithmically transformed (base 10) to normalize the distribution. Skewedness of distributions was assessed with a Kolmogorov-Smirnov test. If a p value < 0.05 was obtained, nonparametric techniques (Spearman's rho for correlation, Mann Whitney U test to compare group means) were applied to analyze the data, values being expressed as median (minimum to maximum). Otherwise, parametric analyses (Pearson's r for correlation, Student's *t* test for comparison of groups means) were used and values were expressed in mean ± SD. Total HDMA exposure to *D. pteronyssinus* was determined by adding up the HDMA exposure to *Der* p I/g and *Der* p II/g. When the HDMA concentration was below detection level, the minimum detection concentration (0.01 µg/g for *Der* p I and *Der* p II) was used for calculations. Seasonal differences in clinical parameters were defined as the autumn value minus the spring value. Multiple regression analysis was performed to obtain a significant model for the seasonal difference in PEF amplitude after withdrawal of ICS as the dependent variable with the seasonal difference in HDMA exposure in the mattress (< -5 µg/g, -5 up to +5 µg/g and > 5µg/g of fine dust) as the independent variable. A p value less than 5% was considered as statistically significant. All analyses were performed with SPSS/PC+ package, version 4.0 (SPSS Inc, Chicago, IL, USA).

Results

Clinical Characteristics

Clinical characteristics of the children are presented in Table 1. Symptom scores, FEV_1, and PEF amplitude were not significantly different between the spring and autumn season. Mean PC_{20} histamine was significantly lower in autumn ($p < 0.05$) than in spring. The total number of eosinophils increased significantly during autumn ($p < 0.05$). PEF amplitudes, total IgE, and specific IgE to HDM were not significantly different between the two seasons.

Seasonal Exposure to Exogenous Stimuli

There was a significant seasonal difference in HDMA exposure due to a higher HDMA exposure in the autumn (Table 1). No significant correlation was found between the magnitude of HDMA exposure and the level of absolute humidity. Smoking habits, presence of pets and floor-coverings did not changed during the study period.

PEF amplitude after withdrawal of ICS

PEF amplitude after withdrawal of ICS in spring and autumn did not significantly correlate with the level of HDMA exposure in the same season (Table 2). However, PEF amplitude correlated significantly and inversely with PC_{20} in autumn (Table 2) and positively with daytime symptoms after withdrawal of ICS in the spring (rho = 0.47; p = 0.01).

Though highest HDMA levels and PEF amplitudes were expected to occur in the autumn, this was not the case in all children (living room n = 7, bed room n = 5, mattress n = 8). Therefore, we calculated whether correlations existed between the seasonal difference in PEF amplitude (autumn value minus spring value) and the other clinical variables.

The seasonal difference in PEF amplitude after withdrawal of ICS correlated significantly and positively with the seasonal difference in total symptom score at night during ICS (rho = 0.44; p = 0.02), inversely with the seasonal difference in FEV_1 after withdrawal of ICS and positively with the seasonal difference both in total HDMA exposure and in mattresses (Table 2). Figure 1 shows that children with a higher seasonal difference in HDMA exposure in the mattresses had higher seasonal differences in PEF amplitude after withdrawal of ICS. Since not all children had the highest HDMA exposure level in the autumn, the Figure also shows negative seasonal differences in HDMA levels and PEF amplitudes.

A multiple regression analysis on the PEF amplitude after withdrawal of ICS showed a significant explaining model (R^2 = 21.0%, p = 0.02) with the seasonal difference in HDMA in the mattress as the only significant contributing variable (Table 3).

TABLE 1 Patient characteristics in spring, autumn and the seasonal differences in clinical parameters (autumn value minus spring value) (n = 25)

	spring	autumn	seasonal difference
FEV_1 % pred +, %	95.8 ± 10.6#	93.7 ± 12.8	-0.6 ± 11.8
FEV_1 % pred -, %	89.7 ± 12.0	87.8 ± 14.0	1.0 ± 13.0
Log_2 PC_{20}, mg/ml	1.38 ± 2.56	0.34 ± 2.23	-1.04 ± 2.19*
Geometric mean PC_{20}, mg/ml	2.60	1.27	0.49
PEF amplitude -, %	23.6 ± 19.1	29.6 ± 15.5	0.7 ± 18.5
Eosinophils, 10^6/l	374 ± 277	561 ± 544	183 ± 424*
Total IgE, IU/ml	315 (20 - 2830)	318 (17 - 1529)	54 (-1379 - 355)
Specific IgE HDM, PRU/ml	28 (1 - 162)	42 (1 - 377)	10.7 (-138 - 215)
Der p I, II in LR, µg/g	0.4 (n.d. - 14.6)	1.2 (n.d. - 24.1)	0.9 (-1.1 - 14.2)**
Der p I, II in BR, µg/g	0.5 (n.d. - 4.1)	0.8 (n.d. - 14.6)	0.3 (-3.3 - 13.0)**
Der p I, II in MA, µg/g	6.1 (0.9 - 115.6)	10.1 (1.4 - 368.8)	1.4 (-111 - 341.8)
Der p I, II total, µg/g	8.6 (1.0 - 119.8)	19.6 (1.6 - 370.0)	9.6 (-112 - 342.9)*

Values are expressed as mean ± standard deviation or median (minimum - maximun) depending on the skewedness of the distribution. +: during inhaled corticosteroids, -: after withdrawal of inhaled corticosteroids, pred: predicted, n.d.: not detectable. Total = *Der* p I and II of living rooms (LR), bedrooms (BR), and mattresses (MA). p: significant seasonal difference (Student's *t* test or Mann-Whitney *U* test, depending on the skewedness of the distribution), *: $p \leq 0.05$, **: $p \leq 0.01$, #: FEV_1 % pred + versus - :$p < 0.001$.

TABLE 2 Correlations between PEF amplitude after withdrawal of inhaled corticosteroids in spring, autumn and seasonal difference (autumn value minus spring value), with clinical parameters and HDMA exposure in the corresponding period

	PEF amplitude after withdrawal of inhaled corticosteroids		
	spring (r or rho)	**autumn** (r or rho)	**seasonal difference** (r or rho)
FEV_1 % pred -, %	-0.05	-0.03	-0.36*
Log_2 PC_{20}, mg/ml	-0.20	-0.45**	0.12
Eosinophils, 10^6/l	0.29	0.22	0.07
Total IgE, IU/ml	-0.03	0.13	-0.07
Specific IgE HDM, PRU/ml	-0.04	0.15	0.05
Der p I, II in LR, µg/g	-0.27	0.20	-0.04
Der p I, II in BR, µg/g	-0.05	-0.09	0.28
Der p I, II in MA, µg/g	0.12	0.20	0.34*
Der p I, II in total, µg/g	0.17	0.11	0.35*

-: after withdrawal of inhaled corticosteroids, pred: predicted. Total = *Der* p I and II of living rooms (LR), bedrooms (BR), and mattresses (MA). Correlation coefficients are performed with parametric (r) or non-parametric (Spearman's rho) depending on the skewedness of the distribution. *: $p < 0.05$, **: $p < 0.01$.

TABLE 3 Multiple regression model for the seasonal difference in PEF amplitude after withdrawal of inhaled corticosteroids (R^2 = 21.0%, p = 0.02)

	ß	p value
Constant	-25.5	0.03
Seasonal difference in HDMA exposure in the mattress	11.7	0.02

HDMA: house dust mite allergen.

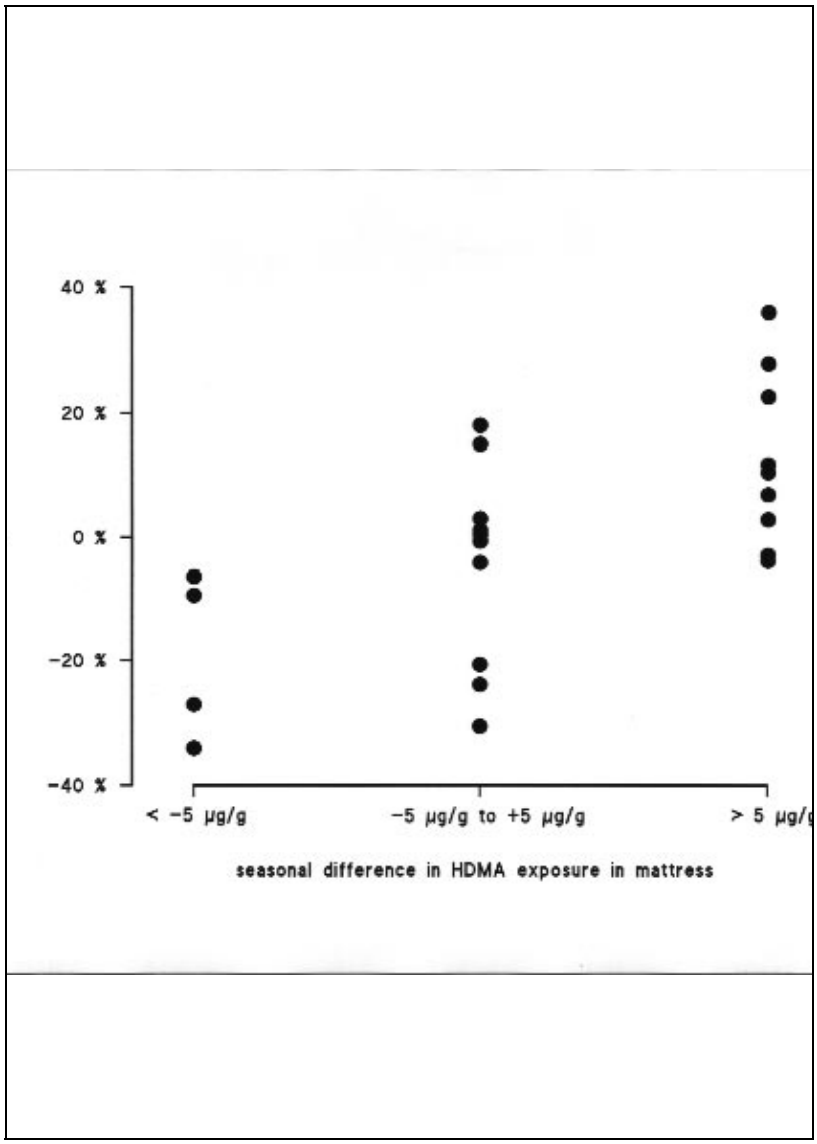

Figure 1 Seasonal difference (autumn minus spring value) in house dust mite allergen (HDMA) exposure of *Der* p I and *Der* p II (µg/g) in mattress and PEF amplitude after withdrawal of inhaled corticosteroids (ICS). Seasonal difference in HDMA exposure is divided in 3 categories (< -5 µg/g, -5 up to +5 µg/g and > 5µg/g of fine dust.

Discussion

This study shows that the absolute level of house dust mite (HDM) allergen exposure is not significantly correlated with the height of the PEF amplitude neither in autumn nor in spring. An important finding is that a larger seasonal change in HDM allergen (HDMA) exposure is associated with a larger change in circadian PEF amplitude. PEF amplitude at a given point in time appears to be determined by more factors than solely the amount of allergen an individual is exposed to. Furthermore our data show that an increase in HDMA exposure in the mattress over seasons enhances an individual's PEF variability.

Our study stresses the fact that mattresses are quantatively the most important source for HDM which affects PEF variability particularly (5,12). In a larger group of HDM-allergic asthmatic children we have previously shown that the occurrence of environmental tobacco smoke, the presence of pets, and high HDMA exposure levels together determine the PEF amplitude in one season to a large extent. This study extends this observation in that changes in exposure levels from the mattresses between seasons are clinically relevant, since they explained 21% of the differences in PEF amplitude between seasons.

Studies from different parts of the world found a seasonal variation in HDMA levels, with highest mean HDMA exposure levels in the autumn months (1,13-16). Our overall results are in accordance with these observations. However, these studies and our results indicate that the variation in exposure levels between seasons can be very small (1,16). Kalra and coworkers observed a statistically significant difference between the seasons (16), but considered the magnitude of the intra individual changes between the seasons small and not of clinical importance. They only measured HDMA concentrations and did not investigate the effect of changes in allergen exposure levels on clinical variables. Our study points to the fact that even relatively small changes in HDMA exposure levels are of clinical relevance for individual patients.

Other studies have emphasized the influence of HDMA exposure levels on clinical variables with regard to disease severity. Zock and colleagues (17) showed in a cross-sectional study that a higher diurnal PEF amplitude correlated with higher HDMA levels collected from carpeted floors. More evidence that HDMA exposure from mattresses is important comes from HDM reduction studies. Ehnert and associates (12) compared the effect of treatment of mattresses with an acaricide and mattress encasements, in allergic asthmatic children. They observed a reduction in the degree of bronchial responsiveness in the group that was treated with mattress encasements. Our data support these findings since we show that spontaneous variations in mattresses HDMA exposure are reflected by changes in circadian PEF variability.

Our observations confirm the findings of an earlier study in HDM-allergic adult patients with asthma (1), in which the increase in HDMA exposure level in autumn

coincided with an increase in bronchial responsiveness. We also found an increase in bronchial responsiveness together with an increased number of blood eosinophils in the autumn months, suggesting that the inflammatory process in the lungs is enhanced in this period of the year. The relationship between increased HDMA exposure levels on one hand, and increased bronchial responsiveness and increased blood eosinophils on the other hand is very likely a causal one since all our children were only allergic to HDM and children with respiratory infections were excluded. However, we did not find this association for PEF variability. Many investigators have suggested that PC_{20} and PEF variability represent both asthma instability and therefore can be used interchangeably. The discrepancy between seasonal changes in PC_{20} which were not reflected in changes in PEF amplitude indicate that both expressions of bronchial lability provide different information on the actual disease state as has been shown in earlier studies by other investigators (18-20).

In summary, we have found measurements of HDMA at a single point of time is not associated with PEF variability in the same season for all individuals. Moreover, we found that seasonal differences in PEF amplitude after withdrawal of ICS correlate significantly and positively with, and are explained to a large extent by the seasonal difference in HDMA exposure in mattresses. Our results amplify the general opinion that reduction of HDMA levels in bedrooms of HDM-allergic children, and especially in mattresses, contributes an essential aspect of the management of asthma.

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